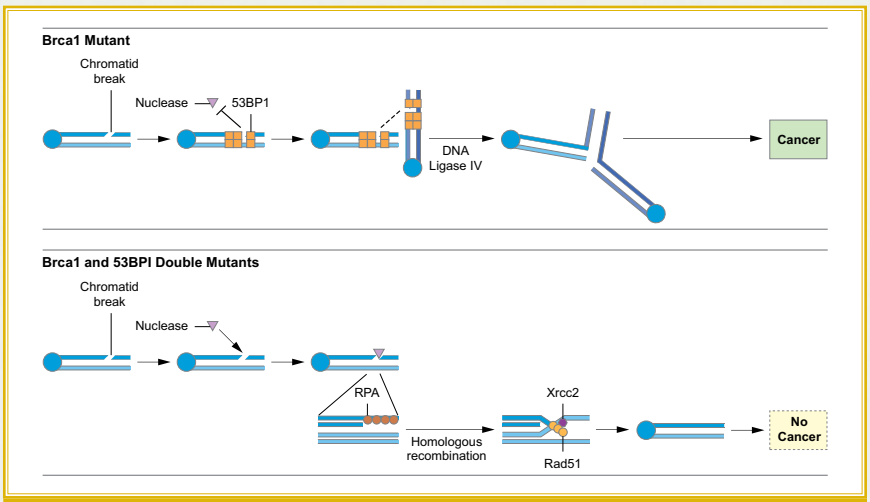
Choose Your Pathway Wisely

Inhibition of the 53BP1 gene restores an error-free pathway for DNA repair that is lost due to a mutation in the oncogene BRCA1.

(Image: J. Kelly)



The 53BP1 protein impairs homologous recombination in BRCA1-deficient cells by blocking a nuclease from generating single-strand DNA necessary for recombination between two homologous DNA molecules. As a result, error-prone DNA repair is mediated by ligase IV. When BRCA1 and 53BP1 are defective, the break is not "clogged," the nuclease can generate single-strand DNA, and homologous recombination can proceed.

Double-strand breaks (DSBs) occur naturally several times a day in every human cell. If left unchecked, they are one of the most mutagenic kinds of DNA damage and have been implicated in many cancers. Homologous recombination (HR)—in addition to producing new combinations of DNA sequences during meiosis—is widely used by cells to accurately repair harmful DSBs. In humans, mutations in the *BRCA1* gene increase the risk of breast and ovarian cancers by impairing HR through incompletely understood mechanisms. Women who carry a harmful mutation in the *BRCA1* gene have up to an 85 percent greater lifetime risk of developing breast cancer than other women, and up to a 40 percent greater chance of developing ovarian cancer.

Mouse *BRCA1*-associated mammary tumors have significant similarities to human *BRCA1*-associated breast cancer in regard to tumor aggressiveness, high incidence, mutations, and genetic instability. In a study published in the April 16, 2010 issue of *Cell*, Andre Nussenzweig, Ph.D., Head of CCR's Molecular Recombination Section of the Experimental Immunology Branch, and fellow NIH investigators as well as colleagues from Rockefeller University and the Spanish National Cancer Research Institute, have compensated for cancer-causing mutations in the *BRCA1* gene in mice by deleting a second gene.

The researchers found that, when a gene known as *53BP1* was also defective, formation of the mammary tumors that normally develop in *BRCA1* mutant mice was suppressed. Moreover, they found that inactivation of *53BP1* restored the DNA repair function that is lost when *BRCA1* is mutated. Using a strain of mice with a defective *BRCA1* gene, the team observed that the mice frequently developed mammary tumors similar to human breast cancers, but tumor formation was largely suppressed when the mice also were lacking the functional protein 53BP1. "This was very unexpected because it was previously believed that BRCA1 was absolutely essential for DNA repair by HR," said Dr. Nussenzweig.

Mechanistically, the team also discovered that both BRCA1 and 53BP1 are capable of binding to replication-associated chromosome breaks; so when both proteins are present, BRCA1 displaces 53BP1, the HR machinery has full access to the breaks, and HR proceeds. In BRCA1-deficient cells, the binding of 53BP1 to the site of DNA damage interferes with the DNA repair activity of HR proteins, so the damage is repaired instead by an alternative pathway that is more prone to producing mutations. When 53BP1 is absent, however, BRCA1 is not needed to displace it so HR can take place normally.

Because BRCA1-deficient tumor cells are forced to turn to other, less faithful DNA repair pathways, the researchers suggest that they may become resistant to chemotherapy by acquiring additional mutations. Such resistance may one day be overcome by therapies to affect pathway choice. "What we've found here is that the choice of DNA repair pathway determines whether the repair is error-free or not," said Dr. Nussenzweig. "This opens the possibility of using drugs to inhibit mutagenic DNA repair pathways and tumor formation."

To learn more about Dr. Nussenzweig's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=nussenzweig.